

Efficacy of High and Low Dose Tranexamic Acid Dosage Regimes for Craniosynostosis Surgery; A Randomized Controlled Non-Inferiority Multicenter Trial.

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Key words: tranexamic acid, antifibrinolytics, craniosynostosis, pediatrics, bleeding, blood loss, blood transfusion.

What is already known: Tranexamic acid is efficacious at decreasing blood loss and blood transfusion in pediatric craniosynostosis surgery.

What this article adds: A tranexamic acid dose regimen of 10 mg/kg loading dose and 5 mg/kg/h maintenance dose is as effective as a higher dose regime of 50 mg/kg loading dose and 5 mg/kg/h maintenance infusion rate in reducing blood loss and transfusion requirements in pediatric craniosynostosis reconstruction surgery.

EXPERIMENTAL DESIGN AND METHODS:

With Internal Research Board and Ethics board approval from the two participating hospitals: (BCH IRB-P00008434) and (GCH Ethic 2013-001056-35) and with informed consent, 68 pediatric patients aged 3 months to 6 years scheduled for open craniofacial surgery were randomized in a prospective double-blind fashion to either the current standard intravenous TXA dose (50mg/kg/15 min and 5 mg/kg/h) or a lower TXA dose (10 mg/kg/15 min and 5 mg/kg/h) until the end of surgery (ClinicalTrials.gov identifier: NCT02188576). A standardized anesthetic and well-defined fluid, blood and blood product management/ transfusion protocol was followed with improved modifications (regarding patient blood management guidelines) from our previously described protocol. CONSORT guidelines for randomized trials were followed.

Patients (age range 3 months to 6 years) undergoing craniosynostosis repair consisting of open cranial remodeling surgery were included (including fronto-orbital advancement surgery, posterior and total calvarial remodeling procedures). Exclusion criteria were patients with a pre-existing active hematological abnormality (defined as a known diagnosis of an active genetic or acquired bleeding disorder/coagulation defect), pre-existing current coagulation defect (defined as screening PT, PTT or INR >1.5 times normal), or acetylsalicylate ingestion within the last 4 days or nonsteroidal anti-inflammatory ingestion with 2 days of the scheduled surgery date. Subjects were recruited in the preoperative clinic by the anesthesia research nurse and, with informed parental and patient consent, were randomly assigned to receive either

intravenous TXA or 0.9% normal saline, according to an investigator blinded computer generated random number sequence

Preoperative data collected included: age, weight, height, gender, race, coexisting diseases, cranial suture(s) involved, preoperative hemoglobin, hematocrit, platelets, PT, PTT, and INR, fibrinogen and blood group. Intraoperative data collected included: estimated volume of blood lost as calculated using the previously validated formula: $ERCV_{lost} = ERCV_{preop} + ERCV_{transfused} - ERCV_{postop}$ ($ERCV$ = Estimated Red Cell Volume)(6) , total surgical time (defined as from incision to last stitch), amount and type of crystalloid and colloid agents administered intravenously, blood product transfusion requirements in the operating room (both total volume and number of exposed units; packed red blood cell, fresh frozen plasma, platelet concentrates, and cryoprecipitate), and total urine output.

Laboratory data was collected at the following times: after arterial line placement for baseline measurements, prior to intraoperative blood product transfusion, at the end of surgery prior to transport from the operating room to the Intensive Care Unit and 24 hours postoperatively and consisted of arterial blood gas, hemoglobin, hematocrit, platelet count, PT, PTT and INR, fibrinogen and d-dimer levels and other biological markers .

Postoperative data collection included surgical drain output, blood transfusion and the occurrence of any postoperative complications. Patients were visited postoperatively daily while in the hospital and a follow-up phone call was made to the family once the patient returned home within 6 months of surgery. These postoperative follow-ups focused on identifying any complications or side effects with specific attention to thromboembolic and neurological side effects.

Statistical Analysis Plan

An *a priori* power analysis indicated that a total sample size of 56 children (28 in randomized each group) would provide 80% statistical power ($\alpha = 0.05$, $\beta = 0.20$) to test whether the difference in average blood loss is equivalent to within 20 mL/kg assuming a standard deviation of 30% (moderate effect size = 0.68) (version 7.0, nQuery Advisor, Statistical Solutions, Saugus, MA). Sixty-eight patients were randomized; 34 per group to ensure sample size requirements were met while accounting for a potential 20% patient drop out. A single randomization list for was used for both sites; BCH and GCH with stratification per site.

The low dosage and high dosage groups are compared with respect to demographics, baseline characteristics, lab values, and intraoperative and postoperative outcomes. Continuous data are presented as mean and standard error or median and interquartile range with comparisons performed using Student's t-test or the Wilcoxon rank sum test as appropriate. Medians and interquartile ranges are presented where the data deviate from normality, including age, weight, length of stay, blood loss and PRBC transfused. Categorical data are presented as frequency and percentage with comparisons made by Fisher's exact test. Mean differences

between the two dosage groups are presented with 95% confidence intervals. For data presented with median and interquartile range, a 95% confidence interval estimate for the difference between comparison groups was obtained using 1000 bootstrap resamples.

Statistical analyses was performed using Stata (version 15.0, StataCorp, College Station, TX). A two-sided alpha of 0.05 was used to determine statistical significance.